Osteoarthritis and Cartilage (1999) **7,** 439–440
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Article No. joca.1999.0248, available online at http://www.idealibrary.com on IDEAL®
1063–4584/99/090439+02 $12.00/0

Osteoarthritis and Cartilage
Journal of the OsteoArthritis Research Society International

Editorial

TGF-β and osteoarthritis: *in vivo* veritas?

Through its associated cartilage breakdown, osteoarthritis (OA) generally results in severe handicap and significant pain. This common joint disease affects about 10% of the world population, including an estimated 50% of people over 60 years of age. By the age of 75, more than 80% of people actually have symptoms of the disease. Approximately 16 million Americans suffer from this condition,[1] and the social cost of the disease has reached impressive figures. Therefore, it is easily understandable that there is considerable research into seeking out effective therapies. Unfortunately, as is often the case for multifactorial diseases, it has been hitherto difficult to clearly define the best target(s) to address, although great progress has been made in the knowledge of cellular and molecular mechanisms underlying cartilage erosion.

The most important discovery in that field was the demonstration, about fifteen years ago, that the cytokine interleukin-1 (IL-1) plays a crucial role in the catabolic process of OA articular cartilage.[2,3] Using in-vitro cultures of synovial cells and chondrocytes, this cytokine (also called 'monocyte cell factor' or 'catabolin' at that time) was shown to be capable of inducing expression of degrading enzymes, the metalloproteases, and suppressing synthesis of the major cartilage matrix macromolecules, collagen type II and aggrecan.[4–7] Since that time, and because of its detrimental effect on cartilage, the IL-1 system and its induced effects on chondrocytes became almost the exclusive target for defining new and future therapeutic approaches. Indeed, considerable efforts are still being made to produce inhibitors of matrix metalloproteases that are induced by IL-1 and/or to reduce the specific binding of IL-1 on the joint cells, taking advantage for example, of the IL-1 receptor antagonist (IL-1 RA) more recently discovered. Interestingly enough, some attempts at genetic therapy in animal models using cells over-expressing IL-1 RA have provided promising preliminary results.[8]

However, an alternative approach to define a new concept of OA treatment should perhaps pay greater attention to the repair potentialities of cartilage and to factors that could antagonize the catabolic and anti-anabolic effects of IL-1. Although adult articular cartilage has got a limited ability to regenerate defects caused by injured or degenerative events, we must bear in mind that studies on the early stages of OA, principally in animal models in which they are easier to investigate, have revealed a repair response of the cartilage to the primary lesions, reflected by activation and clustering of chondrocytes and enhanced proteoglycan synthesis.[9–11] Unfortunately, this process vanishes with time, being progressively overwhelmed by the catabolic events. However, one key issue in developing tools that could favor the repair potentialities of cartilage and perhaps make them last longer, would be to determine the exact role played by local growth factors in these mechanisms and their relationship with cytokines like IL-1. In the recent years, it has been demonstated that TGF-β may play a pivotal role as it can enhance matrix production and modulate chondrocyte proliferation.[12] TGF-β can also counter the IL-1-induced effects on expression of metalloproteases and matrix molecules and down-regulate the expression of IL-1 receptor in articular chondrocytes.[13] However, all these data have been obtained using in-vitro cultures of chondrocytes and, in the absence of information about the in-situ expression of TGF-β and its receptors in the osteoarthritic cartilage, it was rather difficult to conclude about the role this factor plays in the development of the disease.

Interestingly, two recent reports using different approaches make an important contribution towards understanding how changes in the expression of TGF-β receptors on the chondrocyte surface may explain the progressive decrease of the metabolic activity of cartilage and its failure to counter the deleterious IL-1 effects. In the first one,[14] RT-PCR analysis clearly demonstrated that steady-state levels of mRNA for TGF-β receptor type II (TβR-II) are dramatically reduced to almost undetectable amounts at the end of the hypertrophic step of cartilage and at later stages of the degraded tissue in a rabbit OA model (section of cruciate ligament). Given that TβR-II is absolutely necessary to bind TGF-β, before forming a heteromeric complex with TβR-I which transmits the signal,[15] this finding suggests that such down-regulation probably results in reduced sensitivity of the articular chondrocytes to TGF-β during development of the OA process. A diminished responsiveness of OA chondrocytes would explain, at least partially, that repair potential of altered cartilage is no longer capable of balancing the erosive process and that irreversible degradation takes place. This hypothesis recently received strong support from the paper of Serra *et al.*,[16] who have generated transgenic mice that express a truncated, kinase-defective TGF-β type II receptor, acting as a dominant negative mutant, in their skeletal tissue (periosteum/perichondrium, synovium and articular cartilage). They observed that these mice develop a degenerative joint disease resembling osteoarthritis in humans, as judged by histology of the affected joints and alteration of proteoglycan and collagen

Correspondence to: Jean-Pierre Pujol, Laboratoire de Biochimie du Tissu Conjonctif, Faculté de Médecine, Avenue de la Côte de Nacre, 14032 CAEN Cedex, France.

expression. These two reports thus support the idea that loss of responsiveness to TGF-β promotes osteoarthritis and suggest that one of roles of endogenous TGF-β is to maintain the integrity of the articular cartilage and perhaps aid in its regeneration after injury.

So, this recent finding may have some impact on our understanding of osteoarthritis mechanisms and restoration of TGF-β receptor II expression in OA chondrocytes might be a future objective in the treatment of the disease that could delay the degradative evolution of the cartilage, beside the attempts to block IL-1 effects. Since grafts of autologous chondrocytes have been already performed with some sucess to treat cartilage defects of human knees,[17] one can imagine also that, in the future, such chondrocytes could be previously genetically modified to over-express TGF-β receptor II ('super-chondrocytes') and used to repair traumatical injuries of cartilage. Furthermore, it would not be surprising that scientists take advantage of the recent knowledge on molecules implicated in the TGF-β signalling (particularly the *smad* proteins family)[18] to modulate these pathways in order to restore the sensitivity of OA chondrocytes to TGF-β. A new field is perhaps open for chondroprotection and repair of cartilage in joint diseases.

Jean-Pierre Pujol

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